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Review

The disruption of proteostasis in neurodegenerative disorders

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Abstract: Cells count on surveillance systems to monitor and protect the cellular proteome which, besides being highly heterogeneous, is constantly being challenged by intrinsic and environmental factors. In this context, the proteostasis network (PN) is essential to achieve a stable and functional proteome. Disruption of the PN is associated with aging and can lead to and/or potentiate the occurrence of many neurodegenerative diseases (ND). This not only emphasizes the importance of the PN in health span and aging but also how its modulation can be a potential target for intervention and treatment of human diseases.

Keywords: proteostasis; molecular chaperones; unfolded protein response; proteasome; autophagy; therapeutic strategies

Abbreviations: PN = proteostasis network; ND = neurodegenerative disease; AD = Alzheimer´s disease; PD = Parkinson's disease; polyQ = polyglutamine; UPS = ubiquitin proteasome system; HSR = heat shock response; UPR = unfolded protein response; UPR^{er} = unfolded protein response in endoplasmic reticulum; UPR^{mit} = mitochondrial unfolded protein response; ER = endoplasmic reticulum; HSP = heat shock protein; HS = heat shock; *E. coli* = *Escherichia coli*; ATP = adenosine triphosphate; NTD = N-terminal ATPase domain; MD = middle domain; CTD = C-terminal high affinity dimerization domain; AAA+ = ATPase Associated with diverse Activities; ERAD = ER-associated protein degradation; IRE1 = inositol-requiring enzyme; ATF-6 = activating transcription factor 6; PERK = protein kinase RNA-like ER kinase; XBP1 = transcription factor X-box binding protein 1; ERSE = ER stress-response element; JNK = jun amino-terminal kinase; ASK1 = apoptosis signal-regulating kinase 1; eif2 = translational initiation factor 2; ATF4 = transcription factor 4; SIP = site-1 protease; S2P = site-2 protease; *Caenorhabditis elegans* = *C. elegans*; MTS = mitochondrial targeting sequence; ROS = reactive oxygen species; GCN2 = general

control non-repressed 2; PIFK1 = phosphoinositide 4-kinase; K = lysin; CTU = co-translational ubiquitylation; ERAF = ER-associated folding; CMA = chaperone-mediated autophagy; ; mTOR = mammalian target of rapamycin ; ATG = autophagy-related genes; LC3 = light chain 3; LAMP2A = lysosomal membrane-associated protein 2A; Aβ = beta – amyloid; TS = thermo-sensitive; SSBP1 = single-strand DNA-binding protein 1; IIS = insulin⁄ IGF-1 signaling; NFT = HD = Huntington's disease; MJD = Machado-Joseph disease; 17-AAG = 17-(Allylamino)-17-demethoxygeldanamycin.

1. Introduction

To obtain a protein with a stable conformation yet with enough flexibility to serve its function is a challenging task for the eukaryotic cell. Besides the vulnerability to errors during the folding process, proteins have different rates of expression and half-lives, which are continuously influenced by the intracellular and extracellular environment [1, 2]. For these reasons, each cell has to achieve a fine tuning between protein synthesis, folding, trafficking, localization, disaggregation and degradation, in order to ensure proteome quality. The cellular proteome homeostasis, or proteostasis, is achieved by the action of a set of cellular components referred to as the proteostasis network (PN), that prevents accumulation of mutant, misfolded and damage proteins [3] The existence and permanence of misfolded proteins in the cell has deleterious consequences and contributes for many neurodegenerative diseases (ND) such as Alzheimer´s (AD), Parkinson's (PD) and Polyglutamine (polyQ) diseases [4]. A major risk factor shared by these disorders is aging. Indeed, emerging evidence suggest that aging is associated with proteostasis deficiencies, this impairment being now recognized as a hallmark of this physiological process [4, 5].

Central to the PN functionality are the molecular chaperones and their regulators, which prevent protein aggregation either by assisting *de novo* folding and refolding or by driving them for degradation systems, including the ubiquitin-proteasome (UPS) and autophagic systems [6]. This integrated network is regulated by compartment-specific stress sensors that detect an excess of misfolded proteins and respond by activating stress-responsive signalling pathways, such as the heat shock response (HSR), the endoplasmic reticulum unfolded protein response (UPR^{er}) and the mitochondrial unfolded protein response (UPR^{mit}), further discussed below [6–9].

Besides the constant activity of the PN, it seems that there is an inverse relationship between protein aggregation propensity and expression levels, aggregation prone-proteins being more susceptible to decreased synthesis, low abundance and high turnover [10–13].

2. Protein folding

The process of protein folding in eukaryotic cells is highly complex and heterogeneous due to the number of possible conformations that a protein chain can adopt, the existence of a globally high protein concentration ("molecular crowding") with its associated risk of inappropriate intermolecular contacts, proximity to endoplasmic reticulum (ER) membranes and local variations in ionic strength [2, 14–16]. This process also depends on the cooperation of several weak, non-covalent interactions [17]. The free energy required for a polypeptide chain to adopt a functional 3D structure is currently represented as a funnel shape [18, 19] (Figure 1). Unfolded proteins have high free energy and when they start to fold towards the native state, the polypeptide chain explore funnel-shaped potential

energy surfaces by forming intramolecular contacts that restrict the conformational space [17]. Especially for proteins composed of more than 100 amino acids, this process imposes the crossing of substantial kinetic barriers. As a result, partially folded and misfolded states (non-native conformations) that occupy low energy levels may be transiently populated [20, 21]. Proteins at these states tend to aggregate in a concentration-dependent manner due to the exposure of hydrophobic amino acid residues and regions of unstructured polypeptide backbone [22]. Aggregation can lead to either amorphous structures that lack long-range order or to ordered fibrillary assemblies with a free energy minimum even more favourable than the native functional state [23]. Importantly, the formation of fibrillary aggregates is often preceeded by the formation of soluble oligomers, which might be toxic for the cell, giving rise to diseases of aberrant folding, such as ND, systemic amyloidosis and other disorders [24, 25].

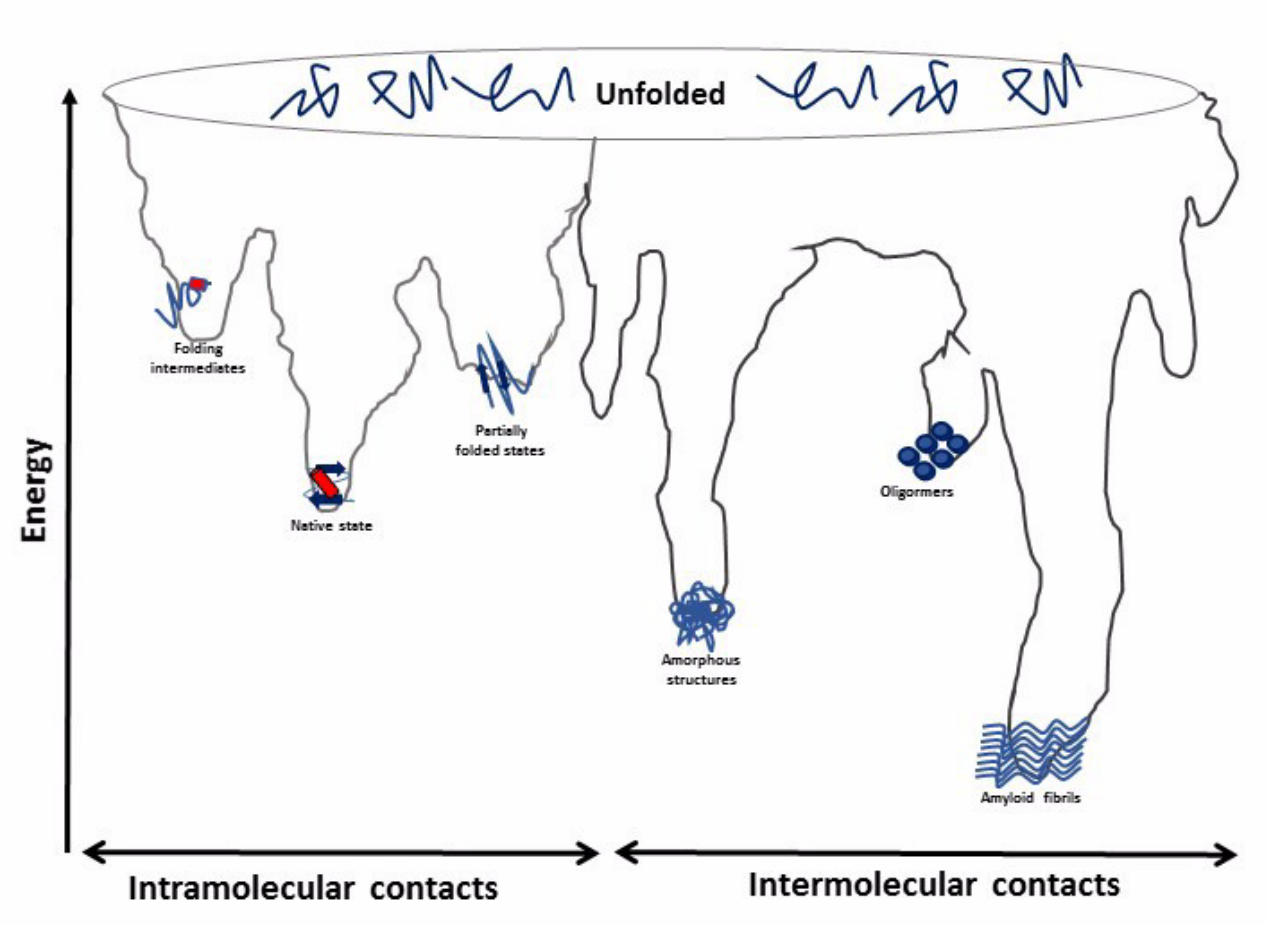

Figure 1. The free energy landscape of protein folding (left) and aggregation (right). Protein folding involves the formation of intramolecular contacts that resemble a partially rough tunnel in which non-native conformations occupy low energy levels. When several proteins fold simultaneously in the same compartment, the intermolecular contacts overlap with the intramolecular contacts resulting in the formation of amorphous structures, toxic oligomers or ordered amyloid fibrils with a lower free energy than the

native state. Molecular chaperomes promotes the folding to the native state. Adapted from [26].

3. Molecular chaperones

By definition, a molecular chaperone is any protein that interacts with and aids in the folding or assembly of another protein without being part of its final structure [27, 28]. First identified as heat shock proteins (HSPs) due to their increased expression upon heat stress (HS), molecular chaperones are divided in six major subclasses according to their molecular size: HSP100s (known as ClpA and ClpB in *Escherichia coli* (*E. coli*)), HSP90s(known as HptG in *E. coli*), HSP70s (known as DnaK in *E. coli*), HSP60s (known as GroEL in *E. coli*), HSP40s (known as DnaJ in *E. coli*), and the small HSPs (known as IbpA and IbpB in *E. coli*), [21, 29, 30].

Members of the HSP60, HSP70, HSP90 and HSP100 families interact either with aggregation-prone, non-native polypeptides or with proteins tagged for degradation [6].

Based on their interaction with client proteins, molecular chaperones can be classified as holdases, foldases and disagregases. Holdases are ATP (adenosine triphosphate)-independent chaperones responsible for the recognition, binding and stabilization of unfolded or partially folded polypeptides and delivery to foldases, avoiding aggregation through a non-catalytic process [31]. Foldases act in refolding of client proteins through ATP hydrolysis. Disaggregases disentangle aggregated polypeptides by ATP hydrolysis and deliver them to holdase and/or foldase for proper refolding [32].

3.1. The HSP70 system

Chaperones from the HSP70 family are central players in proteostasis maintenance [33]. They are abundant and highly conserved chaperones found in all cells, except in certain archaea [34, 35]. HSP70s are located in all cellular compartments (nucleus, cytosol and lysosome: HSP70, mitochondria: HSP70-mt, ER: Bip) [17, 36]. Besides assisting in the folding of newly synthetized proteins and preventing protein aggregation under physiological and stress conditions, HSP70s also play a role in membrane translocation of organellar and secreted proteins, control of the activity of regulatory proteins, and protein degradation [17, 36–39]. This broad spectrum of housekeeping functions is achieved through existence of several specialized HSP70s, both stress-inducible and constitutively expressed, co-chaperones that are selectively recruited by HSP70, and cooperation with other chaperones [40].

Their mechanism of action is ATP-dependent, regulated by chaperones of the HSP40 family and nucleotide-exchange factors, and involves binding and release cycles [41, 42]. Some of the cofactors are also linked to the UPS and autophagy [43].

Nascent chains or stress-denatured proteins exposing their hydrophobic peptide segments are recognized and delivered to ATP-bound HSP70 by HSP40 [26, 44]. The exposure of these fragments correlates with each protein's aggregation tendency [45]. The ATP hydrolysis, accelerated by HSP40, in the N-terminal domain of HSP70 (nucleotide binding domain) causes an alteration in the conformation in the C-terminal peptide binding domain, the latter composed of a helical lid segment and a β-sandwich domain that closes upon ATP hydrolysis forming a clamp [6]. The clamp structure allows a tight binding of the substrate to HSP70. After ATP hydrolysis, a nucleotide exchange

domain protein binds to the HSP70 ATPase domain and dissociates ADP for recycling, resulting in lid opening and substrate release [26]. Upon release, the fast-folding molecules bury their hydrophobic residues and the peptides that need more time to fold will rebind to HSP70, avoiding aggregation. [26] Proteins such as tubulin and actin, which are unable to utilize HSP70 for folding due to high energetic barriers in the folding process, are transferred to the chaperonins [46]. Other proteins, such as signaling proteins, are transferred from HSP70 to the HSP90 system to complete the folding process [47, 48].

3.2. The Chaperonin system

The chaperonin system is unique since it promotes protein folding by enclosing substrates in the inner cavity. Group I chaperonins, also known as HSP60 in eukaryotes, are found in mitochondria and form seven-unit rings. This group functionally cooperates with HSP10 proteins, which form the lid of the folding cage. The Group II chaperonins present in the eukaryotic cytosol (TRiC/CCT) usually form eight-unit rings and are independent of HSP10 factors [26, 49].

Group I chaperonins have a barrel-like structure, comprised of two tightly closed rings that surrounds a large central open cavity. Each ring is composed by an equatorial ATPase domain, an intermediate hinge-domain, and an apical substrate-binding domain. HSP10 is a heptameric ring that closes the ends of the HSP60 cylinder [50]. Briefly, non-native polypeptides are captured through hydrophobic contacts with the apical domain and enter into the central cavity of HSP60 [11, 51]. Upon ATP-binding, HSP10 is recruited by HSP60 and closes the cavity. The binding of ATP causes a dramatic conformational change of the system, creating a highly hydrophylic cage with a net-negatively charged inner wall [28, 52, 53]. In this isolated site the protein cannot misfold due to the inexistence of hydrophobic sites or other proteins for aggregation. During a step of slow ATP hydrolysis, the encapsulated protein is free to fold and leaves the cage after HSP10 dissociation, that is triggered by ATP binding in the opposite ring, or is rapidly captured by another chaperone ring [54].

The Group II chaperonins (TRiC in eukaryotic cytosol) differ from Group I due to the existence of a finger-like protrusion in the apical domain replacing the function of HSP10. These segments open and close through ATP-dependent protein-encapsulation cycles, but at a slower rate than in Group I. This slower rhythm provides a longer period for protein encapsulation and folding [55]. This system interacts with approximately 10% of newly synthesized cytosolic proteins, including actin and tubulin [46, 56]. The substrate transfer to TRiC is mediated by the co-chaperone prefoldin and HSP70, consistent with the general view that chaperones work in a coordinated mannner [57].

3.3. The HSP90 system

The HSP90 family of proteins is highly conserved and accounts for ~ 1–2% of total cellular proteins in non-stressed normal cells, implying that it is part of a fundamental process in biology [58]. The regulatory role of HSP90 chaperones extends to a large variety of cellular processes, including steroid signaling, protein trafficking, calcium signaling, telomere maintenance and nitric oxide signaling, among others [48]. In doing so, HSP90s interact with more than 20 co-chaperones that allow guidance, recognition and modulation of the biochemical activities of client proteins. Indeed, HSP90s are more specialized than other chaperones since they preferentially interact with a specific

subset of the proteome, such as transcription factors and protein kinases. These client proteins are delivered to HSP90s by HSP70 and other co-factors [48].

Although their structure is not completely understood, it is known that HSP90s exist as dimers and are found in almost every compartment of eukaryotic cells. Each monomer consists of an N-terminal ATPase domain (NTD), a middle domain (MD) that modulates binding of client proteins and a C-terminal high affinity dimerization domain (CTD). Similar to other chaperones, HSP90s bind ATP in their NTD, hydrolyzing it. The ATP binding leads to the dimerization of the N-terminal domains, forming a molecular clamp. This closed formation is essential for ATP hydrolysis, after which the N-terminals separate from each other, releasing ADP and the client protein in an active state. There are several co-factors that regulate this cycle by adjusting its kinetic properties in order to achieve certain conformational transitions [59–61].

How HSP90s recruit their client proteins remains to be elucidated, but it is known that these molecular chaperones have several substrate-interaction regions whose binding is strongly influenced by the structural flexibility of the substrate [61]. Indeed, this goes in line with the proposed role of HSP90s as evolutionary capacitor in protecting mutated protein variants from degradation [62].

3.4. The HSP100 system

The HSP100s are a system of molecular chaperones capable to dissolve and reactivate aggregates, among other functions [63–66]. The members of this family are AAA+ (ATPase Associated with diverse Activities) hexameric rings and depending on the number of ATP-binding domains can be subdivided in Class I (two ATP binding domains) or Class II (one ATP biding site) [67–69]. However, the disaggregase activity is only possible if coupled with HSP70 of the same species [70–73]. While yet poorly understood, this activity is required for cell survival after extreme stress conditions, such as high temperatures, that induce protein misfolding and subsequent aggregation [64, 64, 74–77]. In that sense, the cells are capable to recover protein functionality without the energetic and temporal cost that protein degradation demands.

Although higher eukaryotes are also able to perform ATP-dependent protein disaggregation and reactivation, they lack HSP100s. Rather, this function is achieved by a partnership between HSP70, HSP40 and HSP110, which is a non-canonical member of the HSP70 family [77–79].

4. Molecular chaperones and proteostasis

Every time that the cell is challenged with a stress potentially leading to proteostasis impairment, it activates cellular responses, including the HSR (Figure 2). The HRS comprises an adjustment of the expression of chaperones and other cytoprotective genes to ensure stress adaptation, recovery, and survival [2]. Specifically, the HSR reduces the burden of the PN by stopping the synthesis of nonessential proteins and promoting mRNA degradation, while simultaneously increasing the concentration of components of the PN [4].

At the molecular level, this response is a multistep event primarily mediated by HSF1, a highly conserved and ubiquitously expressed transcription factor that is capable of specifically biding to heat shock elements within the promoter of HSP genes [80, 81]. Besides its important role in the activation of the HSR to prevent cell death, HSF1 also monitors chronic proteotoxic stress that affects fecundity and lifespan [82–84]. Nevertheless, it should be highlighted that there are other heat

shock transcription factors in vertebrates whose role is only started to be elucidated [85–88]. In non-stressed cells, HSF1-1 is present as an inert monomer mostly, bound to HSP90, HSP70 and other proteins [89–91]. Upon exposure to stress through competitive binding of an excess of misfolded proteins to HSP90, HSF1 dissociates from the HSP90 protein complex, the export of HSF1 to the cytoplasm is inhibited, leading to increased nuclear accumulation of HSF1 [92, 93]. Activation of HSF1 through trimerization and post-translational events (phosphorylation, deacetylation, sumolyation) leads to binding of this transcription factor to the heat shock element in the promoter region of several molecular chaperone genes to simultaneously induce their expression [93–98]. Various transcriptional cofactors may regulate this step [99, 100]. The resulting increase of cellular concentrations of chaperones, and the action of phosphatases and acetyl transferases in turn inactivates HSF1, in a negative feedback mechanism [82, 89, 101, 102]. In that sense, the duration and intensity of HSR is proportional to the expression of chaperones [103]. The negative regulation of the HSR is of extreme importance in the sense that prolonged over expression of HSPs has been shown to be detrimental to cell growth and division, and to increase susceptibility to cellular transformation [82, 91, 104].

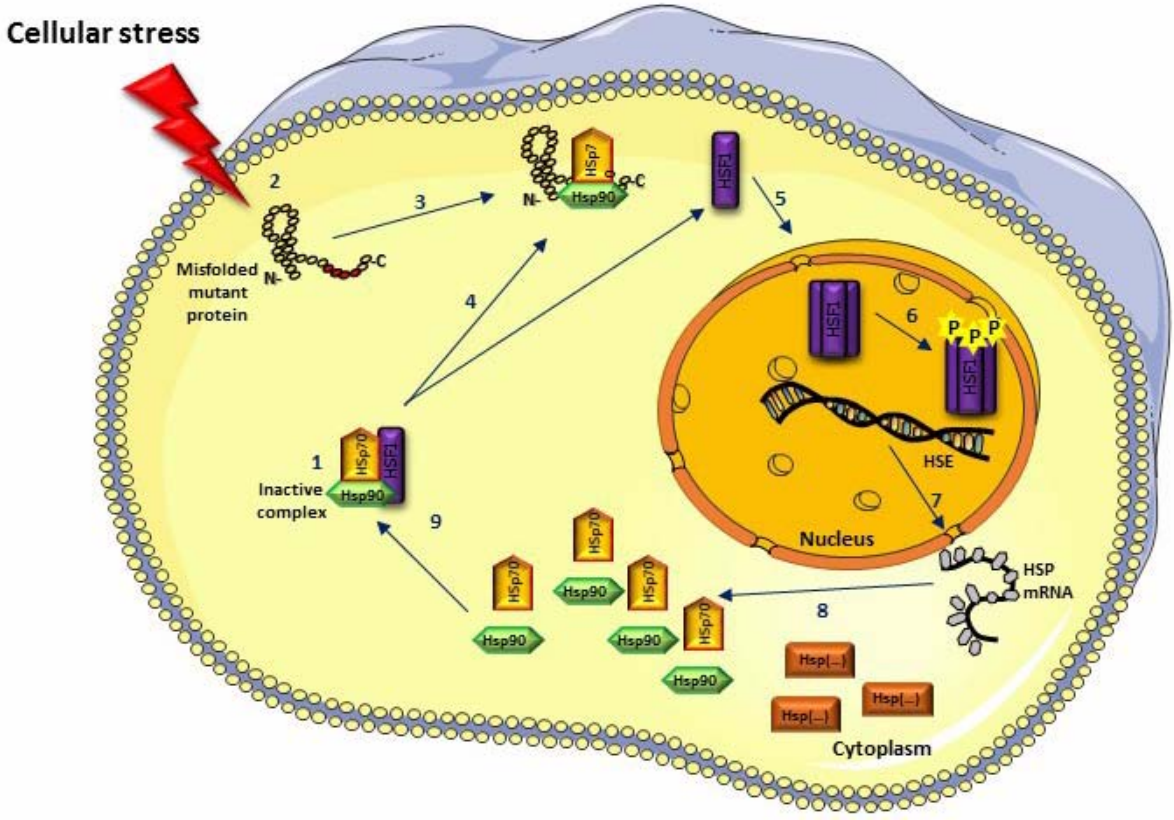

Figure 2. The HSR. Under normal conditions HSF1 is in an inactive form, in a complex with HSP90 and HSP70 (1). The presence misfolded proteins in the cell (2) leads to a displacement of HSP90 and HSP70 of HSF1 to the misfolded proteins and (3, 4). Free HSF1 monomers can then form active trimers and translocate to the nucleus and (5) where it undergoes a series of post-translational modifications (6) and the export to the cytoplasm is inhibited. Once in a competent state, HSF-1 binds to the heat shock response element in the promoter region of several molecular chaperone encoding genes

(7) inducing their expression (8). As the molecular chaperone levels increase, these proteins re-associate with HSF1 inactivating it (9), through a negative feedback mechanism. Adapted from [102].

Molecular chaperones are also involved in the UPR, the functional complement to the HSR in the organelles [103].

The ER is a highly dynamic organelle responsible for the synthesis, processing and trafficking of about one-third of the human proteome [105]. Therefore, the rates of protein synthesis, folding and trafficking must be precisely coordinated in order to ensure that only properly folded proteins exit the ER. Misfolded proteins are either retained within the ER or subject to proteasome dependent ER-associated protein degradation (ERAD) pathway (see below) [106].

The UPR (Figure 3) includes stress sensors located at the ER membrane and transcription factors that act downstream to re-establish gene expression, for adaptation to stress or induction of apoptosis. In mammals, the UPR is mediated by three signalling branches that includes inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6) and protein kinase RNA-like ER kinase (PERK). All the three UPR sensors are regulated by one master regulator, the ER-luminal chaperone GRP78/BIP. When misfolded proteins accumulate in the ER, the binding and sequester of BIP occurs, activating the sensors [9].

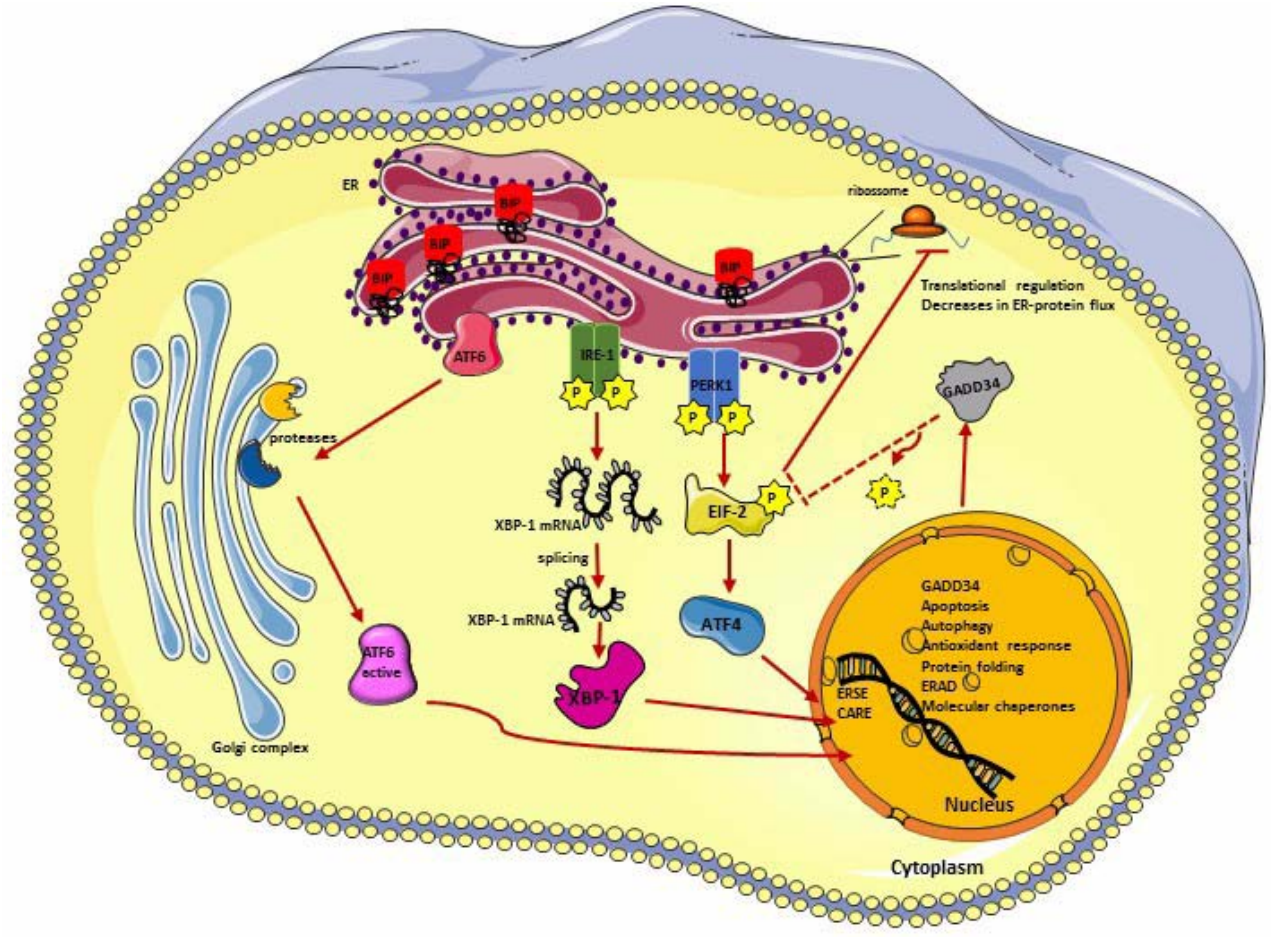

Figure 3. The UPR^{er}. ER stress stimulates the activation of ER stress receptors PERK,

ATF6 and IRE-1 by the chaperone BIP. The activation these three signaling cascades culminates with transcription of ER chaperones, stimulation of protein degradation ERAD and reduction of protein translation. Adapted from [106].

The IRE1 pathway is the most conserved UPR signalling branch [107, 108]. IRE-1 activation by dimerization and its autophosphorylation promotes the splicing of the transcription factor X-box binding protein 1 (XBP1) mRNA [109–111]. Once translated, XBP1 translocate to the nucleus and binds the ER stress-response element (ERSE) in target genes related to protein folding, ERAD, protein translocation into the ER, lipid synthesis and other processes [112]. In addition to splicing XBP1, IRE1 activates JUN amino-terminal kinase (JNK) and the apoptosis signal-regulating kinase 1 (ASK1) pathways, through the binding of adaptor proteins eliciting pro-apoptotic outcomes [113–116].

The translational initiation factor 2 (eIF2) is responsible for translation strand of the UPR. This is mediated by PERK phosphorylation, that attenuates synthesis of new proteins, which would otherwise enter an ER unfavourable for folding and maturation [117–119]. When global protein synthesis decreases and the level of phosphorylated eIF2 is high, the transcription factor-4 (ATF4) is activated [120]. ATF4 binds to CARE promoter to induce a variety of targets genes involved in apoptosis, autophagy, amino acid metabolism, antioxidant response [120–122]. Furthermore, ATF4 activates the expression of GADD34, which de-phosphorylates eIF2 leading to an inhibitory feedback loop, allowing for translational recovery [123–125]. PERK-dependent phosphorylation was also reported to dissociate the Nrf2/Keap1 complex, facilitating Nrf2 nuclear import to induce the expression of antioxidant and detoxifying enzymes [126].

ATF6 is a latent transcription factor located in the ER membrane. Upon ER stress, ATF6 is transported to the Golgi apparatus for proteolytic processing by the site-1 (SIP) and site-2 (S2P) proteases [127]. This releases the transcription-activating form of ATF6 that binds to elements of ER stress-responsive genes encoding molecular chaperones, folding enzymes, and components of the ER-associated degradation system for disposal of misfolded proteins [128, 129].

Although these the branches of the UPR have distinct signalling pathways, they do communicate. For instance, unspliced XBP1 is a negative regulator of both spliced XBP1 and the active form of ATF6, accelerating their degradation in the cytosol [130–132]. Other regulatory crosstalk includes the negative regulation of ATF6 activation by suppression of S1P-mediated cleavage, positive feedback regulation of PERK signalling through a cytosolic splice variant of BIP, inhibitory regulation of PERK by ER co-chaperone up-regulated by ATF6 and XBP1 [133, 134]. Nevertheless, this regulatory signalling is not completely understood.

Analogous to the HSR and the UPR^{ER}, the UPR^{mt} senses and responds to proteotoxic stress by promoting folding, limiting import and reducing translation of mitochondrial proteins [7] (Figure 4). The mitochondria have a preponderant role in cellular metabolic function, which in conjunction with its complex biogenesis makes them particularly vulnerable to accumulating damage during cell life [7]. Although first identified in mammals, the UPR^{mit} has been extensively studied in *Caenorhabditis elegans* (*C. elegans*) [7, 135–139]. When the chaperone capacity is overcome due to the accumulation of unfolded, misfolded or unassembled proteins in the matrix, the proteolytic complex CLPP-1 starts their cleavage into shorter peptides [138]. These peptides are then transported from the mitochondrial matrix into the cytoplasm by the ABC-transprter HAF-1 [140]. The presence of these peptides in the cytosol inhibits mitochondrial protein import, allowing the leucine zipper

transcription factor ATFS-1 to accumulate in the cytosol and traffic to the nucleus [141]. Otherwise, ATFS-1 would be imported into mitochondria via a mitochondrial targeting sequence (MTS), where it would be degraded by the protease LON [141]. In the nucleus, ATFS-1 is responsible for the induction of chaperones, proteases, proteins involved in mitochondrial import, reactive oxygen species (ROS) detoxification and protection against mitochondrial dysfunction, that re-establish proteostasis and restore import efficacy [141]. Additionally, the expression of small ubiquitin-like protein UBL-5 is induced and, together with the homeodomain-containing transcription factor DVE-1, this protein is translocated to the nucleus where it activates HSP-60 transcription [136, 138]. In a complementary pathway, the presence of ROS generated from dysfunctional mitochondria stimulates the general control non-repressed 2 (GCN2) kinase, which phosphorylates eIF2a to slow general translation [142]. Additionally, the phosphoinositide 4-kinase (PIFK1) was recently identified as a common factor essential for the UPR of both mitochondrial and endoplasmic reticulum in *C. elegans* [143].

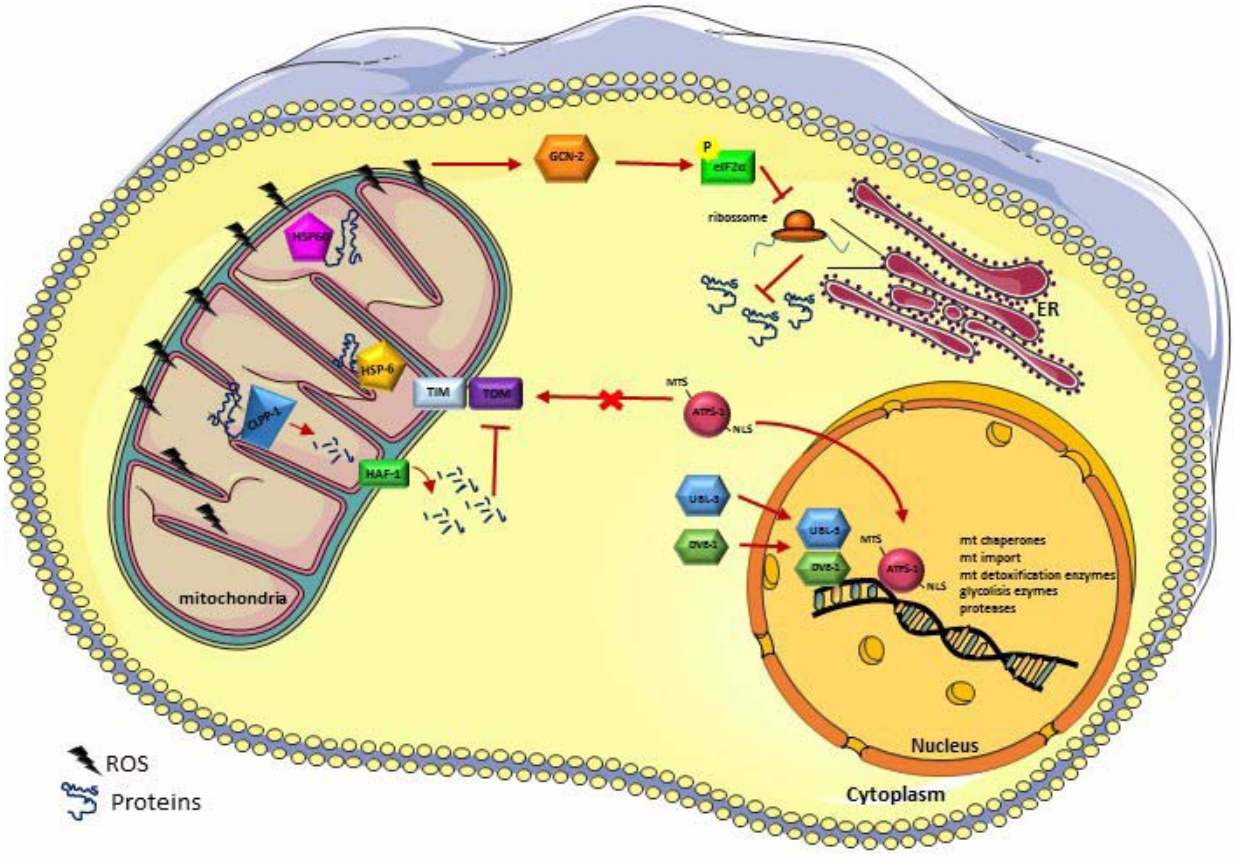

Figure 4. The UPR^{mit} in *C. elegans*. The presence of a mitochondrial stress results in the transcriptional upregulation of protective genes, such as mitochondrial chaperones and proteases. The proteolytic complex CLPP-1 cleaves the unfolded, misfolded or unassembled proteins into shorter peptides that are transported to the cytoplasm by the HAF-1 transporter. The presence of these peptides in the cytoplasm blocks the mitochondrial import of the transcriptional factor ATFS-1, which traffics to the nucleus where, presumably in a complex with small ubiquitin-like protein UBL-5 and

homeodomain-containing transcription factor DVE-1, it activates the transcription of stress response genes, restoring organelle homeostasis. In a complementary pathway, the presence of ROS stimulates GCN2 kinase, which phosphorylates eIF2a to slow general translation. Adapted from [144].

4.1. The nucleus protection against proteotoxic stress

Besides the cytoplasm, ER and mitochondria, the nucleus also has strategies to assure protection from misfolding proteins. The nuclear envelope and nuclear pore complexes can be considered as a first line of defense against proteotoxic stress [145]. Furthermore, the nucleus has specific protein control machineries that can be either nuclear residents or imported from the cytoplasm or ER, which makes the transport pathways crucial to maintain nuclear proteostasis [146]. For example, although the molecular chaperones are mainly cytoplasmic, they can shuttle into the nucleus. Many of them (HSP70, HOP, etc) contain nuclear localization signals and can be imported into the nucleus by RanGTP-mediated mechanism in ambient growth conditions such as cell cycle and import of nuclear proteins [147–149]. Curiously, this kind of transport is transiently downregulated during acute stress [150, 151]. In that sense, the import of misfolded proteins to the nucleus is attenuated, but also the entry of molecular chaperones. Although many other molecular chaperones are imported into the nucleus (HSP90, HSP40, HSP110), it was recently shown that for HSP70 this import is achieved by the protein Hikeshi and independently of RanGTP [152]. Besides acute stress, HSP70, HSP40 and HSP110 are also found in nuclear aggregates caused by aggregation-prone proteins such as mutant huntingtin, ataxin-3 and TDP-43 [153–155]. Even though it remains to be clarified how the nuclear transport of many of these factors is achieved, it is known that this transient association may allow the refolding and disaggregation of these aggregates [156].

4.2. The clearance machinery of the proteostasis network

When a misfolded protein fails to complete the refolding process, it is recognized and degraded through the UPS or through autophagy.

Around 90% of all cellular proteins are degraded by the UPS [157]. This mechanism involves a posttranslational modification in which ubiquitin binds to the proteins, tagging them for proteasomal degradation. This process is achieved by the sequential action of different ubiquitin enzymes that activate (E1; two such enzymes are known in mammals), conjugate (E2; ~ 50–75 in mammals) and ligate (E3; > 500 in mammals) the ubiquitin to the substrate protein [158]. This covalent attachment occurs in a particular lysine (K) residue of the target protein where the carboxyl end of the ubiquitin forms an isopeptide bond [159]. Multiple rounds of this signaling cascade lead to a polyubiquitylated protein that is recognized by the proteasome for degradation. Active proteasomes are multi-protein complexes that consist of a 20S core particle, in which the proteins are degraded and 19S complexes, at one or both ends, that provides substrate specificity and regulation [159]. The proteins targeted for degradation are received by the 19S that assists in its deubiquitylation and unfolding before translocation to the inside of the 20S core particle, where the chymotrypsin-like, trypsin-like, and caspase-like ATP-dependent activities are situated, and cleave the target proteins into short peptides [160]. The fact that the proteolytic activity is located in the inner channel provides protection of the cell against nonspecific degradation [161]. After release, these peptides are either displayed at the

cell surface for immunosurveillance or processed into amino acids for recycling [162, 163]. The UPS also associates with the chaperone machinery. For example, the cochaperone and E3 ubiquitin—protein ligase CHIP binds to with Hsc/HSP70 and HSP90, inhibiting the folding reaction and guiding the faulty client proteins to the UPS [164].

The UPS is also active in the nucleus. Although many of the studies are focused in yeast, higher eukaryotes also have this type of protection [165, 166]. The nuclear UPS is involved in transcriptional regulation, degradation of damaged histones, ribosomal components and nuclear expanded polyQ proteins [167–172].

The ubiquitylation process can have many cellular endpoints besides proteasomal degradation. Indeed, ubiquitin has several K residues (K6, K11, K27, K29, K33, K48, and K63) that can be acceptors of additional ubiquitins [173]. While K11, K29 and K48 signals for proteosomal degradation, K63 chains may participate in transcriptional regulation, signal transduction, DNA repair, endocytosis and degradation through autophagy [173–175]. Furthermore, 12–15% of the nascent proteins are ubiquitylated in K48 through a mechanism termed co-translational ubiquitination (CTU), and sent for proteasomal degradation. This mechanism is potentiated in the context of protein misfolding and represents perhaps one of the earliest quality control system since it tags proteins for degradation before the translation process has finished [176]. The protein ubiquitination state (mono- or poly-ubiquitylated) also dictates if an ubiquitylated substrate is going to degradation or to a non-proteolytic process [177].

As mentioned before, the ER is able to initiate the process of protein degradation through the ERAD pathway. In this process, misfolded proteins in the ER are (1) recognized and (2) targeted for retrolanslocation to the cytosol where (3) they will be degraded through the proteasome. Although largely unknown, the recognition/targeting step is highly controlled and involves a combination of factors (protein energetics, enzyme distribution and metabolism), in the so called ER-associated folding (ERAF) [178]. Is the competition between ERAF and ERAD that determines if a protein is going to be secreted or degraded [178]. Three branches of ERAD pathway have been described in budding yeast, depending on the localization of the misfolding domain relatively to the ER membrane (cytosol, membrane or lumen) [179–181]. However, independently of the branch, all ERAD substrates are ubiquitylated by E3 ligases, in order to be recognized by the cdc48/p97 ATPase complex, responsible for moving the misfolded substrates into the cytosol (retrotranslocation) [182, 183]. At this stage, the ubiquitylated substrates are delivered to the proteasome by shuttle proteins or cytosolic chaperones, for degradation [184–186].

The ERAD pathway function not only for misfolded proteins as proteins, but also for proteins involved, for instance, in sterol biosynthetic pathway, which are targeted for degradation in response to specific metabolic signals [190–193].

Nevertheless, some protein aggregates and cellular contents are too large to cross the proteasome. Instead, they are removed by autophagy, the other major pathway of degradation of the PN. Autophagy is a vacuolar self-digestion mechanism, responsible for the removal of protein aggregates and damaged organelles by the lysosome [187]. There are at least three types of autophagy identified, namely macroautophagy, microautophagy and chaperone-mediated autophagy (CMA) depending on how the substrate is delivered to the lysosome [188].

Some protein aggregates are removed by macroautophagy and CMA [189]. Macroautophagy is the only cellular mechanism able to perform organelle turnover and involves the enclosure of the substrate (a portion of cytosol that may include organelles and/or protein aggregates) in a double

membrane, known as autophagosome [190]. After autophagosome formation, the fusion with the lysosome occurs or, alternatively, the autophagosome fuses first with an endosome (amphisome) followed by a lysosome fusion—forming an autolysosome [190]. The mammalian target of rapamycin (mTOR), a serine/threonine kinase, is crucial for autophagy induction [190]. All this process is further controlled by autophagy-related genes (ATG) categorized in (1) Atg-1/unc-51-like kinase (ULK1) complex, (2) Vps34/classIII phosphatidylinositol-3-phosphate (PI3P) kinase complex, (3) mAtg9 and (4) ATg12 and Atg8/MAP1 light chain 3 (LC3) [190]. CMA is a selective proteolytic system in which specific misfolded proteins exposing a KFERQ-like motif, that otherwise would be buried, is recognized by Hsc70 and co-chaperones [191, 192]. After recognition, the substrates are delivered to the CMA receptor LAMP2A (lysosomal membrane-associated protein 2A) and released into the lysosomal lumen [193, 194]. The lysosome is enriched in hydrolytic enzymes responsible for the degradation of the substrates generating basic metabolites that are released to the cytoplasm [193, 194].

The nervous system is particularly sensitive to autophagy as ablation of Atg genes leads to neurodegeneration [195, 196]. Certainly, neuronal autophagy is crucial for neuronal signaling and synaptic plasticity and the fact that autophagy itself can be a target of neurological disorder suggests that a decrease function of this pathway could be involved in the pathology of these disorders.

4.3. The cell non-autonomous regulation of proteostasis

Since cells of metazoans are part of a complex system, it is plausible to think that there are additional levels of the proteostasis network that control cellular proteome in a non-autonomous manner, otherwise the response in individual cells could interfere with the complex interactions among differentiated cells and tissues and ultimately with organismal survival [197] (Figure 5).

The first evidence pointing to neuronal signalling as a non-cell-autonomous modulator came from studies of Garcia et al., in which defective GABAergic or increased acetylcholine signalling, either genetic and pharmacologically, led to premature polyQ aggregation in *C. elegans* post-synaptic muscle cells [198]. The impact on proteostasis was further assessed using strains expressing thermo-sensitive (ts) mutant proteins, in which it was shown that defective GABAergic signalling led to temperature-dependent phenotypes at permissive temperatures [198]. These results demonstrated the importance of intercellular communication in intracellular proteostasis.

Additional evidence to suggest a more complex level of regulation came from studies in which neuronal signalling was shown to be required for the HSP induction. *C. elegans* has been a model of choice on this matter [199]. In *C. elegans* there are two neurons and interneurons that are responsible to sense fluctuations in temperature, the AFD neurons and the AIY interneurons [200]. AFD-defective animals showed impairment in the HSR after HS [199]. Nevertheless, the expression of HSF-1 and HSP70 was unaltered after exposure to an alternate stress, the heavy metal stress, indicating that this kind of regulation was specific [199]. Besides specificity, this non-autonomous regulation of HSR by AFD neurons was also dependent on the metabolic status. Disruption of temperature and metabolic signal resulted in inhibition of HS-dependent HSP transcription; the presence or absence of both pathways allowed the expression of HSPs upon heat stress [199]. Moreover, this thermosensensory neuronal circuitry appears to be critical specifically for the response to acute stress, as AFD-deficient animals could still activate HSR in peripheral tissues in the presence of a chronic proteotoxic stress, such as that caused by expanded polyQ proteins [201].

Epistasis analysis and calcium imaging suggest that the downstream target of the AFDs was HSF-1 [202]. Data from other studies revealed the chemosensory neurons as additional components of this circuit, capable of activating the HSR, and providing protection against chronic stress such as that caused by the expression of beta-amyloid (Aβ) [203, 204]. These observations opened the question of what the role of the nervous system in organismal regulation of proteostasis is. Specifically, if the HSR induced by the nervous system in peripheral tissues is the cause or the consequence of the macromolecular damage upon heat stress. Recently, it was demonstrated that the AFD thermosensory neuronal activity enhances serotonin release from the serotonergic neurons, initiating a protective activation of HSF1 in non-neuronal tissues [205]. The fact that this release was able to ameliorate the age-dependent accumulation of Q35 aggregates in a *C. elegans* model has important implications for the treatment of proteinopathies [205].

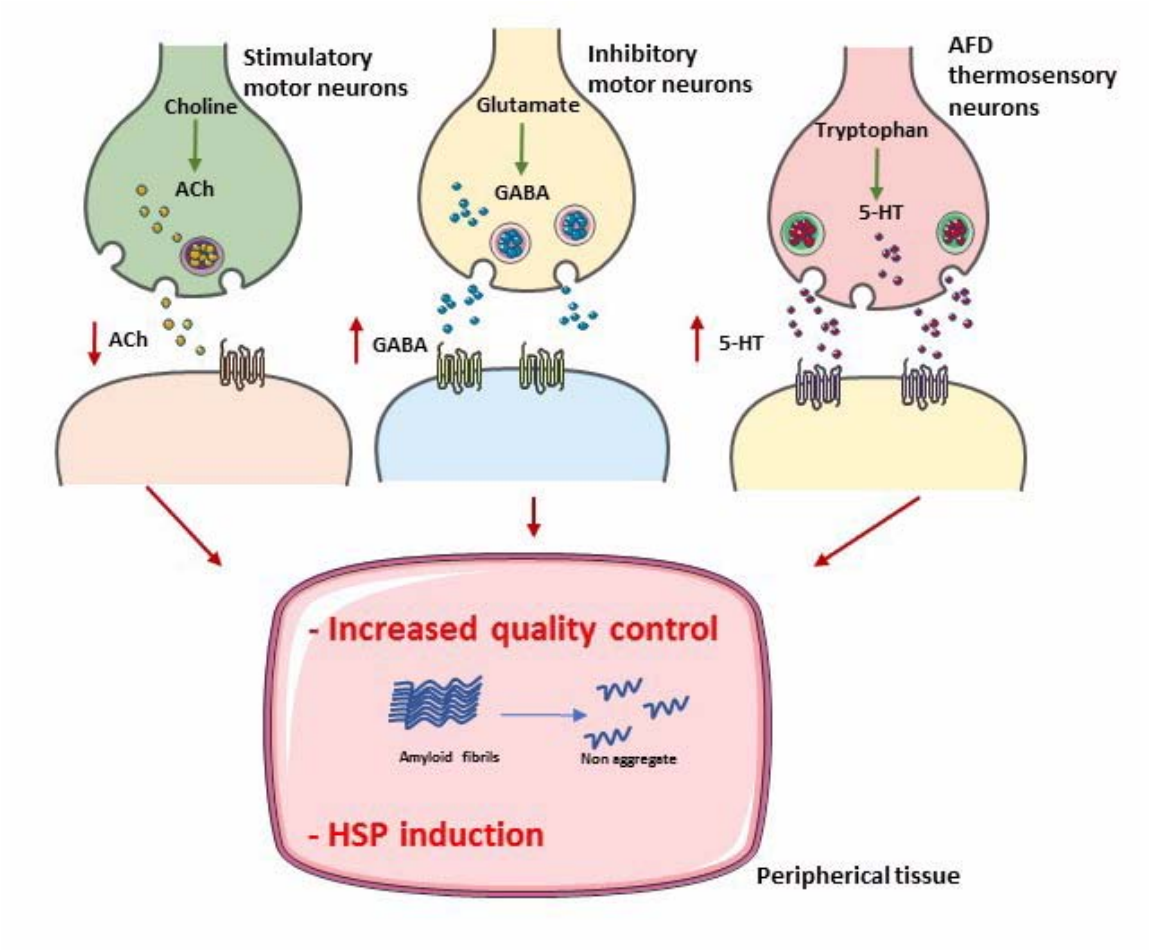

Figure 5. The cell non-autonomous control of proteostasis in *C. elegans*. In the neuronal control system, the increased GABAergic or decrease of acetylcholine signaling and serotonin release promotes protection against proteotoxicity in peripheral (non-neuronal) tissues.

Interestingly, neuronal signals can also directly modify the immune response in *C. elegans* trough G-protein coupled receptors NPR-1 and OCTR-1. The NPR-1 neural circuit is important for the avoidance of certain pathogens and the expression of immune genes in somatic tissues [206].

OCTR-1, a putative octopamine G protein-coupled catecholamine receptor, is able to suppress the innate immune response, which it does by downregulating the expression of non-canonical UPR genes *pqn/abu* in non-neuronal tissues and regulating the p38 mitogen-activated protein kinase pathway [207]. In addition to octopamine, serotonin and dopamine also appear to play a role in the control of immunity [208–210]. OCTR-1 also regulates the canonical IRE-1/XBP1 UPR pathway in adult animals suggesting that the nervous system only starts to control these pathways when the high demand for protein synthesis and folding required in development ends [211]. Consistent with this, the expression of *xbp-1* in the neurons of *C. elegans* activates the UPR^{ER} in the intestine, in a manner dependent on the presence of functional *ire-1* and *xbp-1* in the receiving cells [212]. Intriguingly, the same does not happen if the expression of *xbp-1* is in the intestine. Nevertheless, the expression of *xbp-1* I in neurons protects against ER stress and extends lifespan in the whole organism [212]. Recently it was shown that the expression in intestinal cells of HPL-2, the homolog of heterochromatin 1, a protein involved in epigenetic regulation, rescued the ER stress response, having the opposite effect when expressed in the neurons [213]. The mitochondrial stress response is also under cell non-autonomous control [214]. Specifically, worms with perturbations in the electron transport chain in neurons can induce this stress response in the intestine through the production of a mitokine that is transmitted to the receiving cell [214]. Furthermore, it was recently shown that the HSR modulates mitochondrial signals not only by eliciting the nuclear translocation of a mitochondrial single-strand DNA-binding protein 1 (SSBP1) but also by promoting the expression of mitochondrial chaperones that support cell survival and mitochondrial function under proteotoxic stress conditions [215–217].

Thus, the response to a local proteotoxic stress triggers not only a cell-autonomous protective response but also an increase of chaperone expression in other tissues, to ensure the protection of the organismal proteome [197]. This novel form of stress signalling is only now starting to be revealed. It was recently shown that the disturbance of tissue-specific PN by expression of metastable proteins in muscle induces HSP90 expression not only in the muscle but also in the intestine or neuronal cells [218]. Considering that HSP90s also repress the activity of HSF-1, the non-cell-autonomous regulation of HSP90s must be uncoupled from HSF-1 neural regulation. Indeed, although the pathways involved in the sensing/regulation of HSP90s in the receiving tissues remain, it is known that the transcription factor PHA-4 has a central role as an effector in this type of stress signaling [218]. Together with cell non-autonomous control of proteostasis via neuronal pathways, the transcellular chaperone signaling provides intertissue signaling pathways that monitor and coordinate the proteostasis status between somatic tissues [197].

5. Proteostasis and aging

Aging is the major risk factor for the development of late-onset human neurodegenerative disorders [219]. Although it is not entirely clear why these disorders emerge late in life, it is plausible that the aging process plays an active role in enabling their onset. As organisms age, the tightly regulated balance of gene expression levels, quality control, and protein disposal is disrupted [220]. For example, cellular systems responsible for protein degradation become less efficient with age [221, 222]. In addition, the type of chaperones and co-chaperones that interact in the PN changes during aging and disease [223]. These age-dependent changes in proteostasis are thought to facilitate the aberrant aggregation of specific proteins in the context of neurodegeneration and in a

non-disease context [3]. An emerging concept is that the PN changes early in adulthood to minimize the window of susceptibility to diseases [220, 224].

The fact that proteostasis mechanisms decline with age suggests that manipulating lifespan extension pathways such as insulin signaling may modulate PN in a manner that protects against proteotoxicity and neurodegeneration. The insulin/IGF-1 signaling (IIS) pathway is a prominent aging regulator and lifespan determinant in worms [225, 226], flies [227] and mice [228–230]. This signal transduction pathway has been well characterized in *C. elegans*. The *C. elegans* IIS cascade is initiated when an insulin-like ligand binds to DAF-2, the sole worm insulin/IGF-1 receptor, thereby generating an intracellular signaling cascade [225, 227, 231]. The DAF-2 receptor recruits AGE-1, a phosphatidylinositol 3-kinase that mediates the production of phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P3) [232]. In turn, PtdIns(3,4,5)P3 activates members of the AKT kinase family that phosphorylates and sequesters DAF-16 in the cytosol, which is the sole *C. elegans* FOXO forkhead transcription factor [233, 234]. In contrast, in the absence of ligand or by a mutation in any upstream gene in this pathway, DAF-16 becomes dephosphorylated and then translocates into the nucleus [233, 235]. Upon entering the nucleus, DAF-16 binds to and transactivates/represses numerous target genes involved in life span regulation, stress response, dauer larva formation and metabolism [236–240]. Therefore, the IIS pathway negatively regulates the activity of DAF-16 by modifying its intracellular localization. More recently, a new component of IIS pathway, SKN-1, has been shown to be regulated in similar manner, whereby the nuclear localization of SKN-1 and the transcription of its target genes upon oxidative stress depend on DAF-2 and IIS [241].

The importance of the ILS pathway in determining life span is highlighted by studies showing that the disruption of ILS components results in a dramatically prolonged lifespan. As an example, mutation that decrease the activity of DAF-2 or AGE-1 in *C. elegans* more than double the lifespan of the animal and increase stress resistance [225, 242–246]. DAF-16 is critically required for reduced IIS to mediate longevity in worms, as daf-16 knockdown abolishes the increase longevity of daf-2 mutants [225, 247].

HSF-1 is also essential for lifespan extension since inhibition of HSF-1 function leads to decreased life span and an accelerated aging phenotype in *C. elegans* [243]. Conversely, overexpression of HSF-1 extends lifespan [245]; this extension is facilitated by reduced IIS [83]. Furthermore, transcriptional profiling of genes regulated by HSF-1 and DAF-16 has revealed that these two transcription factors share a subset of target genes, including HSP-12 and HSP-16 encoding small HSPs, important players in both lifespan extension and protection from proteotoxicity [245]. In addition to the overall life span extension, worms bearing either of these mutations are highly resistant to oxidative stress [248], hypoxia [249], heat stress [242], heavy metals [250] and bacterial pathogens [251].

These findings support the notion that aging is a genetically regulated process and that mutations in longevity-linked genes delay the onset of decline, with a major contribution of the PN [244].

6. Proteotoxicity and neurodegeneration

Neurodegenerative disorders, including AD, PD and polyQ diseases, are characterized by progressive dysfunction and loss of neurons and synapses in specific (vulnerable) areas of the

nervous system that determines the clinical presentation and course [252]. They represent a major public health concern in Western Societies since they usually appear late in life and life-expectancy has increased in the last century. The social and financially consequences that impose have made the research on these disorders a priority worldwide.

AD is a multifactorial progressive neurodegenerative disorder in which both extracellular amyloid plaques, consisting of aggregated Aβ peptide, and intracellular neurofibrillary tangles (NFTs), containing aggregated, hyperphosphotylated tau are the pathological hallmarks [253]. Parkinson's disease is the second most common age-related neurodegenerative disease, characterized by an accumulation of α-synuclein in Lewy bodies [254]. PolyQ diseases, including Huntington's disease (HD),Machado-Joseph disease (MJD) and Spinal and bulbar muscular atrophy (SBMA)', are a group of nine late-onset neurodegenerative disorders characterized by the presence of expanded CAG repeats within the coding region of the corresponding disease genes [255]. Although the proteins involved in these diseases do not share functional and structural homology, they share common protein aggregation pathology, that has led to the hypothesis of protein misfolding as one of the main mechanisms that lead to disease [3, 256]. It has been suggested that the chronic expression of misfolded proteins and the resultant stress that they generate overload the PN and clearance mechanisms, further accelerating its aging-related decline and leading to neurodegeneration. Moreover, recent evidence also indicates that the disease-associated/causing aggregates may continue to amplify and spread to previously unaffected areas which may help to explain the gradual progression of these disorders [257].

Several are the examples that show the proteostasis impairment in neurodegenerative diseases, especially for polyQ disorders. By using *C. elegans* as a model system it was demonstrated that the onset of polyQ toxicity coincides with in age-dependent collapse of proteostasis [258]. Other studies have shown that in HD and MJD the disease protein associates with members of the HSR through a combination of sequestration and transcriptional dysregulation [259]. These findings suggest a model in which the chronic expression of proteins with an abnormal polyQ tract leads to global proteome disruption through chaperone depletion/competition [260]. Moreover it is important to recognize that each cell type has its specific chaperone network that may react differently to the presence of misfolded proteins. For example, for the same polyQ tract length in *C. elegans*, the intestinal cells are more vulnerable to aggregation and toxicity than neuronal cells [258, 261]. Furthermore, in different neurons the polyQ tract may show different aggregation patterns[258]. This neurospecificity was recently shown in a *C. elegans* model of MJD [262]. Together, these differences pinpoint the importance of efficient stress responses and the subsequent elevation of specific chaperones to deal with chronic expression of misfolded proteins.

In support of this hypothesis, restoration or enhancement of the PN through improvement of the chaperone capacity should ameliorate the detrimental consequences of the presence of misfolded proteins[6]. Indeed, the overexpression of chaperones or co-chaperones in different models of polyQ diseases had positive impact on pathogenesis either by decreasing aggregate formation, enhancing mutant protein degradation and partitioning of mutant protein into less toxic structures, among other outcomes [263–266]. Consistently, knockdown of chaperones and PN regulators results in early onset aggregation [262, 267].

Nevertheless, PN improvement can be achieved by other pathways that do not involve molecular chaperones or by the classical stress responses. For example, DNJB6b and DNAJB8, members of HSP40 family, suppresses expanded polyQ aggregation and toxicity by

HSP70-independent means [268]. Inactivation of MOAG-4/SERF, a small protein discovered through a *C. elegans* RNAi screen for modifiers of polyQ aggregation, suppress the formation of compact polyQ aggregation intermediates independently of the proteasome, autophagy or HSF-1-induced molecular chaperones [269]. The action of MOAG-4 was further confirmed for other neurodegenerative diseases [269]. More recently it was shown *in vitro* that human SERF1a, a short isoform of SERF, regulates proteotoxicity by selectively binding with α-synuclein amyloid precursors and accelerating the amyloid aggregation [270].

As explained above, another emerging concept is the dysregulation of stress response transcription factors as an important of neurodegeneration disease pathogenesis [271]. In cellular and mouse models of HD, non-aggregated polyQ-expanded huntingtin blocks the induction of the HSR under stress conditions, compromising cellular proteostasis [272]. Alteration of the chromatin architecture, reduced HSF1 binding and perturbed HSF1-dependent gene expression have been considered important factors for the abnormal HSF1 response after stress [272–274]. The disruption of the HSR has been described not only for HD but also for other several neurodegenerative diseases [262, 275–277]. In the same way, DAF-16/FOXO3a is also impaired in several neurological conditions [262, 275, 278]. The protective role of this transcription factor in HD mice seems to due to an increase of activity of SIRT1 [279]. As mentioned above, SIRT1 also impacts the HSR by deacetylation of HSF1 [98]. Recently, novel regulators of HSF1 acetylation were identified namely, AROS and DCB1 [280]. Both are SIRT1 modulators and regulate HSF1 differently. AROS overexpression increases HSF1 recruitment to the *HSP70* promoter, while DCB1 has the opposite role [280]. Nevertheless, the mechanism by which HS may regulate SIRT1 is still unknown.

7. Proteostasis drug targeting in neurodegenerative disorders

Given the compelling evidence supporting the protective role of many PN components in NDs, efforts have been made in order to make PN a drug target for these diseases.

Given the pivotal role of HSF1 in proteostasis maintenance, several are the approaches under development that target the activation of this transcription factor. This has been achieved in several ways, including with compounds that selectively bind to HSP90s, repressing the negative feedback mechanism of the HSR [281]. Geldanamycin, a naturally occurring HSP90 inhibitor, was able to ameliorate the phenotype and accumulation of misfolded proteins in several neurodegenerative disease models by inducing the expression of chaperones [282–284].

17-(Allylamino)-17-demethoxygeldanamycin (17-AGG), a geldanamycin analogue, was also successful in inducing the expression of HSP's and supressing neurodegeneration in *Drosophila* models of MJD and HD [285]. 17-(Dimethylaminoethylamino)-17-demethoxygeldanamycin (17-DMAG) is a more potent derivative of 17-AGG, more water soluble than 17-AGG and can which be administered orally, thus making it a more feasible long-term therapeutic agent [286–288]. Likewise, 17-DMAG was also proven to be a good therapeutic agent for other polyQ diseases [262, 289, 290]. Interestingly, the induction of the HSR is not the only way through which HSP90s can exert a positive outcome. For instance, in the case of SMBA models, 17-AAG mitigates the neurological phenotypes by direct destabilization and subsequent degradation of mutant androgen receptor, which is a natural client of HSP90, and independently of HSR action, since the protective effect takes place even in HSF1 knock-out cells [291, 292]. Leucine-rich repeat kinase 2, which is mutated in both familial and sporadic cases of PD, and PTEN-induced kinase 1, a protein involved in

autosomal recessive form of familial PD, are both client proteins of HSP90, whose inhibition leads to their proteasomal degradation [293, 294]. The levels of tau protein are also diminished by the proteasome after treatment with HSP90 inhibitors, since tau, and some kinases responsible for its phosphorylation on pathogenic sites (GSK3*β*, CDK5, Akt) are HSP90 client proteins [295, 296]. For α-synuclein and ataxin-3, the positive impact of 17-AAG and 17-DMAG respectively, was shown to be in part due to activation of the autophagic pathway and regulation of synaptic plasticity [290, 297, 298]. Collectively, these reports represent an important proof-of concept regarding the use of HSP90 inhibitors in neurodegenerative diseases. However, it is important to recognize that the use of HSP90 inhibitors may have side-effects, with potential cytotoxicity due to clearance of other HSP90 client proteins and the continuous activation of the HSR. Recent screens have identified compounds that activate HSF1 in a way that is independent of the HSP90 interaction. HSF1A is a HSF1 activator able to protect against toxicity in cell and fly models of HD and MJD by binding to the TRIC/CCT chaperonin system, and may be a promising complementary approach [299, 300]. More recently, a ~ 1,000,000 compound screen for novel HSR activators identified a barbituric acid-like compound (F1) which was able to rescue the folding stability of proteins involved in conformational diseases, in both cell and worm models [301]. In spite of the subtle induction of gene expression by F1, there was an activation of multiple stress responses to restore PN [301].

Since stress-dependent HSF1 activation can be deleterious, efforts have also been channeled in the development of strategies that promote the activation of this transcription factor independently of the stress. As a proof of concept, a ligand-regulated HSF1 that was able to be activated in the absence of stress was recently described [302]. This stress-independent HSF1 activation increased cellular proteostasis with minor impacts on cellular proteome function and prevented intracellular aggregation of misfolded proteins [303]. This idea opens new avenues in PN enhancement drug discovery. Finally, modulation of aggregation through activation of degradation pathways such as the UPS and autophagy is also actively being pursued, as revised elsewhere [304].

8. Conclusion

A functional PN is extremely important for the organismal survival and normal nervous system function, and its therapeutic modulation has been proven to be efficacious against several misfolded protein-related neurodegenerative diseases. Although many players of the PN are only now starting to be identified, this will lead to new ways of clinical intervention with important repercussions for our society.

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Conflict of Interest

All authors declare no conflicts of interest in this paper.

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